Original research

Periprocedural unfractionated heparin bolus during endovascular treatment in acute ischemic stroke does more harm than good

Johannes Wischmann, Ilias Masouris, Linus Keidel, Steffen Tiedt, Christoph G Trumm, Hanna Zimmermann, Thomas Liebig, Günter Höglinger, Lars Kellert, German Stroke Registry-Endovascular Treatment (GSR-ET) Investigators

ABSTRACT

Background Unfractionated heparin (UFH) bolus is occasionally administered during endovascular treatment (EVT) to reduce thrombotic complications in acute ischemic stroke patients. However, the MR CLEAN-MED trial showed an increase in symptomatic intracranial hemorrhages (SICH) and a non-significant shift towards worse functional outcome with UFH administration. We aimed to analyze the impact of periprocedural UFH bolus in a real-world setting in anterior (ACS) and posterior circulation stroke (PCS) patients.

Methods We analyzed data from the German Stroke Registry-Endovascular Treatment using propensity score matching. Primary outcome was the modified Rankin Scale at 3 months, and secondary outcome measures included mortality, angiographic outcomes, post-EVT National Institute of Health Stroke Scale scores and ICH at 24 hours.

Results Among 13,082 patients, 7948 with ACS (UFH bolus use in 15%) and 841 with PCS (UFH bolus use in 16.3%) were included in the propensity score matching analysis. Applying MR CLEAN-MED study criteria, UFH bolus was associated with worse functional outcomes (odds ratio [OR] 1.44; 95% CI 1.06–1.96). Analyzing all ACS and PCS patients, UFH bolus did not provide any net benefit. In ACS patients treated with intravenous thrombolysis (IVT), UFH bolus use was associated with worse functional outcomes (OR 2.40; 95% CI 1.34 to 5.06).

Conclusion Our findings show transferability of the MR CLEAN-MED results into a real-world setting, confirming a negative effect of periprocedural UFH on functional outcome in this subgroup of patients. Considering all ACS and PCS patients, periprocedural UFH did not provide a net benefit and appears to be harmful, particularly in IVT-treated patients.

INTRODUCTION

In acute ischemic stroke caused by large vessel occlusion (LVO), antithrombotic medication is occasionally used during endovascular therapy (EVT) to prevent thrombotic complications and improve angiographic outcome. Unfractionated heparin (UFH) is one such medication that is used intravenously as a bolus and in flushing solutions during EVT to reduce thrombus formation on wires, stents, and catheters, optimize microvascular perfusion and eliminate hypercoagulability in cerebrovascular patients. However, the administration of periprocedural UFH may be linked to increased rates of bleeding complications. Consequently, it is subject to ongoing discussion whether this undermines the antithrombotic efficacy when evaluating clinical outcomes. Observational studies have analyzed the possible net benefit of UFH during EVT in anterior circulation stroke (ACS) patients on functional outcome, but results have been heterogeneous.

Current guidelines do not provide specific recommendations for the use of periprocedural UFH during EVT, and its use is often at the discretion of the interventional radiologists.

In 2022, the “Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands investigating the effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither” (MR CLEAN-MED) study...
was published, the first randomized controlled trial (RCT) assessing the safety and efficacy of periprocedural UFH in anterior circulation LVO stroke patients. The study found that UFH was associated with an increased risk of symptomatic intracranial hemorrhage (sICH) without evidence of a beneficial impact on functional outcome, and the trial was terminated early due to safety concerns. Follow-up vessel imaging after 24 hours revealed higher rates of complete recanalization in UFH patients, which did not seem to outweigh the disadvantageous effect of UFH. However, no RCT is available that analyzes the effect of periprocedural heparin in posterior circulation stroke (PCS) patients.

In this analysis, we aimed to assess the efficacy and safety of UFH bolus during EVT in a large observational dataset of ACS patients, applying the major inclusion criteria of the MR CLEAN-MED trial to assess its transferability to a real-world patient population. We expected to find more specific results than the non-significant trends observed in the MR CLEAN-MED trial, given the larger patient cohort. Additionally, we planned to analyze the effect of UFH bolus in all ACS patients and assess its efficacy and safety in PCS patients. Our study aimed to provide insight into the use of UFH bolus during EVT in acute ischemic stroke patients and thus to support the clinical decision-making process.

METHODS

Study population

Data were obtained from the German Stroke Registry-Endovascular Treatment (GSR-ET), which has been described in detail elsewhere. Briefly, the GSR-ET (ClinicalTrials.gov Identifier NCT03356392) is a prospective, multicenter registry designed to evaluate the outcome, safety, and periprocedural parameters of adult LVO acute ischemic stroke patients who undergo EVT. The registry enrolled patients consecutively from 25 centers in Germany. Clinical decisions for treatment with EVT and/or intravenous thrombolysis (IVT) were based on current national and international guidelines. UFH was carried out with alteplase applying 0.9 mg/kg body weight over 1 hour (10% bolus). Tenecteplase was not used in any participating center. Clinical and radiological data of all patients were rated and assessed by local neurologists and neuroradiologists at each site. Functional independence before and after the qualifying stroke was assessed using the premodified Rankin Scale (pmRS) and the modified Rankin Scale (mRS), respectively. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Radiological early signs of cerebral infarction were assessed using the Alberta Stroke Program Early CT Score (ASPECTS), while the degree of reperfusion was rated using the Thrombolysis In Cerebral Infarction (TICI) score. Antiplaquette therapy included medication with aspirin and/or clopidogrel, while oral anticoagulation included medication with apixaban, rivaroxaban, edoxaban, dabigatran, and phenprocoumon. During EVT, a bolus of UFH was applied in addition to heparin rinse solutions. All data were checked for plausibility, integrity, and completeness using a standardized protocol, and queries were sent to the respective centers in cases of inconsistent data.

Inclusion criteria

The data for this study were collected from adult patients who received EVT between June 2015 and December 2021. To classify patients as having either an anterior or posterior circulation stroke, the type of vessel occlusion was determined using baseline CT angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). Patients for whom no data were available on whether an additional bolus of UFH was administered during EVT, or who received other intravenous or intra-arterial antithrombotic medication during EVT, were excluded from the analysis. After applying these inclusion criteria, a total of 9712 patients were enrolled for consecutive analyses. Figure 1 provides an overview of the patient selection process.

To analyze ACS patients based on the MR CLEAN-MED inclusion criteria, individuals with a pmRS of 0–2 and NIHSS of ≥2 who underwent groin puncture within 6 hours of known stroke onset (SO) were included, resulting in a total of 3172 patients. To expand the scope of the analysis to include all ACS patients, regardless of pmRS, NIHSS, or time from SO to groin puncture, a total of 7948 patients were enrolled.

For the analysis of PCS patients, only those with basilar artery occlusion in baseline cross-sectional imaging and DSA were included, resulting in a total of 841 patients.

For the analysis of all ACS and PCS patients, cases in which the time of stroke onset (SO) was unknown were included. The median time between “last seen well” and “time of recognition” was used to calculate the time interval.

Outcome and safety parameters

The primary outcome parameter was the mRS shift after 3 months. Secondary outcome parameters included successful reperfusion (TICI score of 2b-3), complete reperfusion (TICI score of 3), NIHSS after 24 hours and at discharge, and mortality. Intracranial hemorrhage (ICH) was defined as a safety parameter. ICH was defined as any intracranial hemorrhage in postinterventional intracranial imaging after 24 hours, regardless of the presence or absence of new neurological deficits.

Statistical analysis

Propensity score matching was carried out, using logistic regression analysis based on age, sex, pmRS, NIHSS at baseline, and IVT status to estimate the propensity score with a caliber of 0.2. One-to-one nearest neighbor matching was used, matching patients with periprocedural UFH bolus administration to patients without UFH bolus administration. Age, sex, pmRS, NIHSS, and IVT status were well balanced between both groups in all three cohorts. After propensity score matching, univariate analysis was carried out, comparing parameters between patients with (UFH+) and without (UFH−) administered additional heparin bolus during EVT. Each variable is displayed with mean±SD, median±IQR, or counts and percentages, where applicable. Variables were checked for normality, using the Kolmogorov–Smirnov test. Differences between UFH+ and UFH− patients were compared, using the Mann–Whitney U test, the chi-squared test and Fisher’s exact test, where appropriate. To determine association with outcome and safety parameters, ordinal, binary logistic, and multiple linear regression models were used where applicable. Variables that are either known to impact outcome and safety parameters or were different between groups in univariate analysis were included as baseline characteristics in adjusted regression models. Effect estimates were displayed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 26 for Windows (IBM Corp., Armonk, NY, USA).
RESULTS

Univariate analyses

MR CLEAN-MED cohort

Univariate analyses were conducted on all ACS patients who met the major inclusion criteria for the MR CLEAN-MED study (n=643) (see online supplemental table 1). Of these patients, 61.4% (n=395) received an additional heparin bolus during EVT (UFH+), while 38.6% (n=248) did not (UFH–). The median number of applied heparin units was 4360 IU (3000–5000 IU). The time interval from SO to door was longer in UFH+ patients (95 vs 80 min; p≤0.05), while the time interval from door to reperfusion was comparable (110 vs 100 min; p=0.19). Extracranial stenting was required more frequently in UFH+ patients (17.2 vs 5.6%; p≤0.05).

All ACS patients

With respect to all ACS patients (n=1592), 74.7% (n=1190) received a heparin bolus during EVT (UFH+) and 25.3% (n=402) did not (UFH–). The median number of applied heparin units was 5000 IU (3000–5000 IU). Overall time intervals were longer in UFH+ patients and distribution of risk factors was different between both groups. The rate of extracranial stenting was comparable between both groups (12.0 vs 9.5%; p=0.17) (see online supplemental table 2).

All PCS patients

In the PCS patient group (n=239), n=137 (57.3%) received a heparin bolus during EVT (UFH+), while n=102 (42.7%) did not (UFH–). The median number of applied heparin units was 5000 IU (3000–5000 IU). Door to reperfusion (149 vs 113 min; p≤0.05) and groin to reperfusion (45 vs 25 min; p≤0.05) time intervals were longer in UFH+ patients, while all other time intervals were comparable between both groups. UFH+ PCS required more retrieval attempts for vessel reperfusion compared with UFH– patients (2 vs 1; p≤0.05) (see online supplemental table 3).

Outcome and safety parameters

MR CLEAN-MED cohort

In ACS patients who met the major inclusion criteria of the MR CLEAN-MED study (table 1), mRS shift analysis demonstrated a significant shift towards worse functional outcomes after 3 months in patients who received an additional heparin bolus during EVT (OR 1.44; 95% CI 1.06 to 1.96; p≤0.05; figure 2A). Of 643 patients, the mRS at 3 months was available for 551 (85.7%) patients. Furthermore, multiple linear regression analyses revealed that additional heparin during EVT was associated with an approximately three-point increase in the NIHSS after 24 hours (ß=2.74; 95% CI 1.08 to 4.40; p≤0.05) and approximately three points higher NIHSS at discharge (ß=3.13; 95% CI 1.41 to 4.89; p≤0.05). NIHSS at 24 hours and at discharge was available for 95.8% and 91.4% of patients, respectively.

All ACS patients

For all patients with ACS (table 1), mRS shift analysis revealed no effect of periprocedural UFH bolus on functional outcome (OR 1.13; 95% CI 0.88 to 1.45; p=0.36; figure 2B). Notably, mRS data were available for 74.2% (n=1182) of patients at 3 months. However, multiple linear regression analyses revealed
Table 1  Multivariate regression analysis of outcome and safety parameters for heparin bolus administration during endovascular treatment in anterior circulation stroke (ACS) patients (MR CLEAN-MED inclusion criteria), all ACS patients and all posterior circulation stroke patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACS patients (MR CLEAN-MED inclusion criteria)</th>
<th>All ACS patients</th>
<th>All PCS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) β (95% CI) P-value</td>
<td>OR (95% CI) β (95% CI) P-value</td>
<td>OR (95% CI) β (95% CI) P-value</td>
</tr>
<tr>
<td>mRS shift at 3 months*</td>
<td>1.44 (1.06 to 1.96) &lt;0.05</td>
<td>1.13 (0.88 to 1.45) 0.36</td>
<td>0.64 (0.32 to 1.30) 0.21</td>
</tr>
<tr>
<td>TICI 2b-3 reperfusion†</td>
<td>0.60 (0.25 to 1.43) 0.25</td>
<td>1.13 (0.65 to 1.94) 0.67</td>
<td>1.36 (0.49 to 3.76) 0.56</td>
</tr>
<tr>
<td>TICI 3 reperfusion†</td>
<td>0.96 (0.63 to 1.46) 0.84</td>
<td>0.97 (0.74 to 1.28) 0.84</td>
<td>1.08 (0.51 to 2.27) 0.84</td>
</tr>
<tr>
<td>NIHSS at 24 hours§</td>
<td>2.74 (1.08 to 4.40) &lt;0.05</td>
<td>2.19 (1.03 to 3.35) &lt;0.05</td>
<td>1.95 (–2.06 to 5.96) 0.39</td>
</tr>
<tr>
<td>NIHSS at discharge§</td>
<td>3.15 (1.41 to 6.9) &lt;0.05</td>
<td>3.67 (2.32 to 5.01) &lt;0.05</td>
<td>1.40 (–2.71 to 5.51) 0.50</td>
</tr>
<tr>
<td>Mortality at 3 months*</td>
<td>0.86 (0.47 to 1.55) 0.61</td>
<td>1.01 (0.70 to 1.46) 0.95</td>
<td>0.75 (0.35 to 1.57) 0.44</td>
</tr>
<tr>
<td>ICH at 24 hours§</td>
<td>0.91 (0.50 to 1.67) 0.76</td>
<td>0.69 (0.48 to 1.02) 0.06</td>
<td>2.74 (0.36 to 20.81) 0.33</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, pmRS, NIHSS, IVT, ASPECTS, BP diastolic, heart rate, hypertension, AF, dyslipidemia, SO to door, groin to reperfusion, SO to groin, type of vessel occlusion, retrieval attempts, and extracranial stenting (ACS patients with MR CLEAN-MED inclusion criteria); adjusted for age, sex, pmRS, NIHSS, IVT, door to groin, groin to reperfusion, door to reperfusion, risk factors; and overall complications (all ACS patients); adjusted for age, sex, pmRS, NIHSS, IVT, hypertension, diabetes, dyslipidemia, groin to reperfusion, door to reperfusion, number of passages, and ICH at 24 hours (PCS patients).

†Adjusted for age, sex, pmRS, NIHSS, hypertension, diabetes, dyslipidemia, BP systolic, ASPECTS, SO to door, door to groin, groin to reperfusion, carotid T occlusion, IVT, extracranial stenting, and retrieval attempts (ACS patients with MR CLEAN-MED inclusion criteria); adjusted for age, sex, pmRS, NIHSS, IVT, risk factors, door to groin, door to reperfusion, and groin to reperfusion (all ACS patients); adjusted for age, sex, pmRS, NIHSS, IVT, hypertension, diabetes, door to reperfusion, groin to reperfusion, and retrieval attempts (PCS patients).

‡Adjusted for age, sex, pmRS, NIHSS, ASPECTS, BP diastolic, heart rate, hypertension, AE dyslipidemia, SO to door, groin to reperfusion, SO to groin, type of vessel occlusion, reperfusion attempts, and extracranial stenting (ACS patients with MR CLEAN-MED inclusion criteria); adjusted for age, sex, pmRS, NIHSS, IVT, risk factors, door to groin, groin to reperfusion, door to reperfusion, and overall complications (all ACS patients); adjusted for age, sex, pmRS, NIHSS, IVT, diabetes, hypertension, dyslipidemia, groin to reperfusion, door to reperfusion, retrieval attempts, successful reperfusion, and ICH at 24 hours (PCS patients).

§Adjusted for age, sex, pmRS, NIHSS, IVT, ASPECTS, BP diastolic, heart rate, hypertension, AF, dyslipidemia, SO to door, groin to reperfusion, SO to groin, type of vessel occlusion, retrieval attempts, and extracranial stenting (ACS patients with MR CLEAN-MED inclusion criteria); adjusted for age, sex, pmRS, NIHSS, IVT, risk factors, door to groin, door to reperfusion, and door to reperfusion (all ACS patients); adjusted for age, sex, pmRS, NIHSS, IVT, diabetes, dyslipidemia, hypertension, door to reperfusion, groin to reperfusion, retrieval attempts, and successful reperfusion (PCS patients).

ß, beta coefficient; ACS, anterior circulation stroke; AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; CI, confidence interval; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PCS, posterior circulation stroke; pmRS, premodified Rankin Scale; SO, stroke onset; TICI, Thrombolysis In Cerebral Infarction.
Figure 2  Modified Rankin Scale (mRS) shift analysis and distribution of mRS at 3 months for unfractionated heparin (UFH) bolus during endovascular treatment (EVT) in anterior circulation stroke (ACS) patients (MR CLEAN-MED major inclusion criteria) (A), all ACS patients (B), all posterior circulation stroke (PCS) patients, (C) and all intravenous thrombolysis (IVT)-treated ACS patients (D). Patients with additional UFH bolus during EVT (UFH+) are compared with patients without additional UFH bolus during EVT (UFH–). A significant shift towards worse functional outcomes was observed in UFH+ ACS (A) (OR 1.44; 95% CI 1.06 to 1.96; p≤0.05). No significant mRS shift was measured when analyzing all ACS patients (B) (OR 1.13; 95% CI 0.88 to 1.45; p=0.36). In PCS patients (C) no effect of periprocedural UFH on the mRS shift was observed (OR 0.64; 95% CI 0.32 to 1.30; p=0.21). In ACS IVT-treated patients (D) we measured a shift towards worse functional outcomes (OR 2.40; 95% CI 1.34 to 5.06; p<0.05).
that a heparin bolus during EVT was independently associated with higher NIHSS scores at 24 hours (β=2.19; 95% CI 1.03 to 3.33; p=0.05) and at discharge (β=3.67; 95% CI 2.32 to 5.01; p<0.05). NIHSS data at 24 hours and at discharge were available for 82.1% (n=1307) and 78.5% (n=1249) of patients, respectively.

All PCS patients
In the PCS patients analysis (table 1), periprocedural UFH bolus was not significantly associated with outcome and safety parameters (figure 2C).

Effect of heparin bolus during EVT in ACS patients with (IVT+) and without (IVT–)
In patients with ACS who received IVT, heparin bolus during EVT was associated with a significant shift towards worse functional outcomes (OR 2.40; 95% CI 1.34 to 5.06; p<0.05; figure 2D). No effect of heparin bolus during EVT on mRS shift was detected in ACS IVT– patients (table 2).

DISCUSSION
In this study, we analyzed real-world data of patients with ACS and PCS who underwent EVT and assessed the effects of periprocedural UFH bolus administration on functional outcome and safety parameters. Our main findings are summarized below.

First, an additional UFH bolus during EVT was administered in 15.1% of all patients in our unmatched cohort. In IVT-treated patients, periprocedural UFH bolus was used in 12.1%. We found UFH to have an overall negative effect on functional outcome in ACS patients when applying the major MR CLEAN-MED inclusion criteria to our study cohort. When analyzing all ACS patients, periprocedural UFH bolus administration did not provide a benefit and rather was associated with higher NIHSS scores at 24 hours and at discharge.

Second, we found that periprocedural UFH bolus administration had no effect on functional outcome and safety parameters in PCS patients.

Third, we found periprocedural UFH bolus administration to be associated with increased odds for worse functional outcomes, particularly in IVT-treated ACS patients. Periprocedural UFH bolus administration did not provide a benefit in ACS patients not treated with IVT.

The MR CLEAN-MED investigators found that heparin was associated with an increased risk of sICH without evidence of a beneficial impact on functional outcome.12 However, the mRS shift analysis demonstrated a non-significant shift towards worse functional outcome in heparin-treated patients. Additionally, a trend towards higher NIHSS scores after 24 hours and at discharge was also observed in these patients, which is likely linked to higher rates of sICH. Although we estimated significant effects on these parameters in our analysis, caution is necessary when interpreting our findings as the amount of heparin administered varied between patients during EVT. Unlike the MR CLEAN-MED trial, where patients received a constant infusion of either 1250IU/hour or 500IU/hour of UFH for 6 hours following a 5000IU bolus, our cohort received a single bolus of approximately 3000–5000IU. However, we did not find a dose-effect relationship in our cohort. Our findings when analyzing all ACS patients are consistent with the growing evidence that UFH during EVT does not provide a benefit in ACS patients. However, previous literature has shown heparin to be safe and beneficial for functional outcome, raising the question of whether this switch of effect is linked to the use of more modern state-of-the-art stent retrieval devices, which were also used in our cohort.7 13 14 Notably, heparin did not affect distal embolization in our analyses, contrary to previous postulations that heparin-related clot and thrombus softening could increase the risk of embolization.15 However, we observed lower rates of distal embolization in general in our cohort compared with other observational studies, which may have affected this finding.

Regarding the use of periprocedural heparin specifically in PCS patients, there are sparse data available as most observational studies did not solely focus on PCS patients.7 13 15 Currently, there are no RCTs available assessing the safety and efficacy of periprocedural heparin in PCS patients. However, an observational data analysis from the Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke (ANGEL-ACT) registry identified heparin during EVT to have a negative effect on functional outcome in patients with acute vertebrobasilar occlusion.16 Therefore, further controlled studies specifically for PCS are needed.

While the main strength of this analysis lies in its prospective, large-sample, and multicenter design, it is not without limitations. First, based on our study cohort data, we were unable to definitely distinguish between any ICH and sICH in follow-up cerebral imaging. However, in our analyses UFH bolus administration during EVT consistently predicted for neurological worsening, which may be linked to a higher rate of sICH in UFH-treated patients. Second, we were unable to provide data about specific heparin dosages applied via flushing and rinse solutions during EVT which, however, was also not considered as a potential confounder in the MR CLEAN MED trial. Third, we decided to exclude patients with other intravenous and/or intraarterial periprocedural medication from our analyses to primarily focus on the sole effect of UFH which does, however, limit our ability to assess the potential effects of other antithrombotic substances.

CONCLUSIONS
Our study shows a negative association between periprocedural UFH bolus during EVT and outcomes and safety. The possibility of a differential effect of UFH bolus between
ACS and PCS patients requires further investigation. Our findings support those of MR CLEAN-MED in a large, real-world patient population.

Twitter Steffen Tiedt @SteffenTiedt

Collaborators Study group name: German Stroke Registry-Endovascular Treatment (GSR-ET) Investigators. The individual names are listed in the supplementary files (Supplementary material [study group]).

Contributors JW and LK conceptualized the study. JW, LK, ST, and HZ collected the data. JW carried out the analysis and wrote the first draft of the manuscript. All authors commented on draft versions of the manuscript and read and approved it in its final form. JW is responsible for the overall content as guarantor. The guarantor accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

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ORCID iDs
Johannes Wischmann http://orcid.org/0000-0003-0653-943X

Steffen Tiedt http://orcid.org/0000-0002-8817-8457

Christoph G Trumm http://orcid.org/0000-0002-1249-3338

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